REMARKS

The Office Action mailed December 1, 2004 has been received and reviewed. The application is to be amended as set forth. Claims 1-3, 9-11 and 33-50 were rejected. Claims 1 and 4-12 have been canceled. Claims 13-32 have been withdrawn. Claims 2, 37, 40, 43, 46, and 50 are currently amended. Claims 2-3 and 33-50 are currently pending and under examination. All claim amendments and cancellations are made without prejudice or disclaimer. Reconsideration of the application is respectfully requested.

OBJECTION TO THE DRAWINGS

The drawings stand objected to as per PTO form 948. Correction of the informalities identified in the drawings are submitted herewith.

SUPPORT FOR THE CLAIM AMENDMENTS

Support for the claim amendments can be found throughout the specification and the claims.

INFORMAL OBJECTIONS

Claim 2 is objected to for the alleged informality that a verb is missing and that "is" should be inserted prior to "adapted." Applicants have reviewed the referenced lines of the claim (lines 10-12) and are of the opinion that the language of the claim does not require insertion of "is," but is not changed by the insertion of the word. Therefore, claim 2 has been amended as suggested by the Examiner.

REJECTIONS UNDER 35 USC § 112

Claims 2, 37, 40, 43, 46 and 50 are currently amended. The Office objected to claims 2, 37, 40, 43, 46 and 50 on the basis that "the metes and bounds of a gene sequence encoding at least a part of a penton and/or hexon protein (fiber)(shaft and knob) are unclear". (Page 3 of

Office communication) The term "gene sequence" has been amended to "nucleotide sequence". Applicants submit that the substitution of the term "nucleotide sequence" will clarify "encoding at least part of a penton and/or hexon protein (fiber) (shaft and knob)".

Applicants request reconsideration of the rejection under 35 U.S.C. § 112, second paragraph, for claims 2-3, 37, and 40-48 as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention in lieu of the currently amended claim 2 upon which claim 3 is dependent; claim 37; claim 40, upon which claims 41 and 42 are dependent; claim 43, upon which claims 44 and 45 are dependent; claim 46, upon which claims 47 and 48 are dependent. By amending "gene sequence" to "nucleotide sequence", Applicants definitely and particularly claim the subject matter which Applicants regard as the invention.

The Office rejects claim 50 under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, the omitted step being "how a chimeric adenoviral particle can be "provided" with a gene sequence encoding a tail region." Given the current amendment to claim 50, amending "gene sequence" to "nucleotide sequence", Applicants submit that the chimeric adenoviral particle can be provided with a nucleotide sequence through commonly used genetic engineering techniques of the art.

Reconsideration and withdrawal of the rejection are respectfully requested.

REJECTION UNDER 35 U.S.C. §103(a)

The Office maintained the rejection of claims 1-3, 9-11, and 33-50 as being assertedly unpatentable over U. S. Patent 6,127,525 to Crystal et al. ("Crystal") in view of PCT International Patent Publication WO 96/26281 to Wickham et al. ("Wickham") under 35 U.S.C. § 103(a).

Crystal *et al.* teaches construction of a chimeric capsid protein (specifically, the hexon protein of the capsid) as a means of avoiding neutralizing antibodies (*see*, Crystal *et al.* at col. 3, lines 35-56). For example, Crystal *et al.* specifically describes providing "a chimeric adenovirus

coat protein (particularly a chimeric adenovirus hexon protein) comprising a **nonnative amino acid sequence**. The chimeric adenovirus coat protein is not recognized by, or has decreased ability to be **recognized by, a neutralizing antibody directed against the corresponding wild-type (i.e., native) coat protein**" (Crystal *et al.* at col. 3, lines 59-65; *see also* col. 4, lines 3-7; col. 4, lines 42-46 describing avoiding antibodies directed against a native coat protein) (emphasis added).

Moreover, Crystal *et al.* stresses the importance of the chimeric coat protein as being other than a native sequence, by defining "chimeric," as used in the phrase "chimeric coat protein," to be a sequence "that is **not** typically found in the protein as isolated from, or identified in, wild-type adenovirus .... The chimeric coat protein thus comprises (or has) a 'nonnative amino acid sequence'" (Crystal *et al.* at col. 5, line 58-64). The importance of the "non-native" sequence is even further elaborated on in at least columns six through eleven of the specification, which refer entirely to chimeric capsid proteins (primarily the hexon protein). Therefore, the importance of changing the amino acid sequence of a capsid protein to avoid neutralizing antibodies is highly evident in Crystal *et al.*

Hence, Crystal *et al.* does not teach "that the adenovirus coat proteins can be modified by deleting and replacing a region of the coat proteins ... with the corresponding region from another adenoviral serotype," as asserted by the Office (*see*, page 5 of the Office Action). Because of the emphasis placed on avoiding neutralizing antibodies, which are directed against the corresponding wild-type (*i.e.*, native) coat protein, Crystal *et al.* teaches away from the use of native fiber protein sequences. Specifically, neutralizing antibodies are directed against wild-type coat proteins and the purpose of Crystal *et al.* is to avoid neutralizing antibodies.

Furthermore, according to Crystal *et al.*, exchanging the fiber protein does not avoid the neutralizing antibody response (col. 25, lines 15-19), and the "hexon protein, and to a lesser extent the fiber protein, comprise the main antigenic determinants of the virus" (col. 2, lines 46-52). Thus, a person of ordinary skill in the art is left with the conclusion that switching the fiber

protein would produce no useful result. Hence, using a chimeric fiber protein composed of two native sequences is contrary to the purpose of Crystal *et al.*

In contrast, the applicants have demonstrated that specific serotypes of adenovirus face at least a significantly reduced neutralizing antibody response. For the first time the applicants have demonstrated that native capsid proteins from the claimed serotypes can avoid neutralizing antibodies, without all of the effort required to produce the chimeric capsid of Crystal *et al.* Essentially, the chimeric capsid proteins disclosed in Crystal *et al.* are inapplicable to the applicants claimed chimeric fiber proteins.

Furthermore, a single generic reference to restriction sites (*e.g.*, col. 17, lines 62-66 of Crystal *et al.*) cannot be combined with unrelated generic statements regarding mutating, deleting or inserting sequences (*e.g.*, col. 14, lines 15-19) and a laundry list of all known adenoviral serotypes (col. 4, lines 32-41) to produce an enabling disclosure of a chimeric fiber protein comprising the tail region derived from the native serotype of the recombinant adenoviral vector and a stem and/or knob region from an adenovirus serotype selected from the group consisting of 11, 14, 16, 21, 34, 35, and 50. Placement of the passages cited by the Office in the order of citation, produces the following:

> A "coat protein" according to the invention is either an adenoviral penton base protein, an adenoviral hexon protein, or an adenoviral fiber protein. Preferably a coat protein is a adenoviral hexon protein or an adenoviral fiber protein. Any one of the serotypes of human or nonhuman adenovirus can be used as the source of the coat protein, or its gene or coding sequence. Optimally, however, the adenovirus coat protein is that of a Group B or C adenovirus and, preferably, is that of Ad1, Ad2, Ad3, Ad5, Ads, Ad7, Ad11, Ad12, Ad14, Ad16, Ad21, Ad34, Ad35, Ad40, Ad41, or Ad48. (col. 4, lines 32-41) Briefly, the method of mutagenesis comprises deleting one or more regions of an adenovirus coat protein, and/or inserting into an adenovirus coat protein one or more regions with a differing amino acid sequence, particularly by manipulating the DNA

> sequence. (col. 14, lines 15-19) Similarly, the means of constructing such a transfer vector are known to those skilled in the art. For instance, a chimeric adenovirus coat protein gene sequence can simply be ligated into the vector using convenient restriction sites. (col. 17, lines 62-66).

However, the applicants submit that the cited passages are too widely dispersed and unrelated to the actual teaching of Crystal *et al.* be properly combined into the teaching that is asserted by the Office. The broadest possible interpretation of the cited passages is that there are numerous adenoviral serotypes that may be used as a source of a coat protein, and that coat proteins may be made as chimeras using methods known in the art. Crystal *et al.* does not teach or suggest retaining the tail region from a first adenovirus serotype and a stem/knob region from a second adenovirus serotype. In fact, Crystal *et al.* teaches that exchanging the fiber protein does not reduce antigenicity.

Thus, Crystal *et al.* can not provide motivation for the use of the claimed chimeric adenoviral fiber protein to avoid neutralizing antibodies, especially in light of Crystal *et al.*'s disclosure that exchanging the fiber protein has no effect on the ability of neutralizing antibodies to recognize the chimeric adenovirus (*e.g.*, col. 25, lines 15-19)[1]. Hence, Crystal *et al.* teach away from exchanging the fiber protein, including producing the presently claimed chimeric fiber protein, to avoid neutralizing antibodies or to alter tropism.

The Office acknowledges that Crystal *et al.* does not teach that the chimeric fiber protein will also be responsible for exhibiting a desired tropism. Hence, even assuming for the sake of argument that every teaching the Office asserts were to actually be found in Crystal *et al.*, as a bare minimum for the establishment of an obviousness rejection Wickham *et al.* must, at the very least, teach or suggest that the claimed adenoviral serotypes produce a different tropism. Wickham *et al.* does not teach or suggest even that bare minimum.

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[1] "These results confirm that switching the fiber from that of adenoviral serotype 5 group C vector to that of an adenoviral serotype 7 group B vector by itself is insufficient to allow the vector to escape neutralizing antibodies generated against an adenoviral vector comprising Ad5 fiber" (col. 25, lines 15-19 of Crystal *et al.*).

Wickham *et al.* does not provide the missing teaching or suggestion, or overcome the teaching away present in Crystal *et al.* Wickham teaches that there is a high degree of similarity amongst the fiber molecules from different serotypes, for example, "Ad2 and Ad5 fiber proteins ... both likely bind to the same cellular receptor" (page 3, lines 30-32 of Wickham *et al.*). The Office also asserts that the exchange of Ad5 and Ad7 fibers, as performed in Wickham *et al.*, have altered tropism, as shown by Gall '96 (page 8 of the Office Action). Gall '96 states in the cited passage that "the receptor numbers, binding affinities, and virus entry pathways **are functionally similar** for dlAd5NCAT and dlAd5NCAT-F7 (Gall, (1996) *J. Virol.*, page 2119, col. 2, paragraph 3). Gall '96 further report "[o]ur studies on gross infections of the heart, liver, and lung suggest that the majority of cells available for infection in all likelihood contain receptors for both Ad5 and Ad7 present in functionally equal numbers" (*Id.* at p. 2121, first column, last paragraph). Thus, Gall '96 does not demonstrate that the Ad5/7 chimeric fiber has a different tropism. Therefore, Wickham does not teach that using different fiber molecules from different serotypes would result in different tropisms. For example, Wickham *et al.* states that "[b]ased upon the high degree of structural similarity between the fiber molecules of the more than 41 human serotypes of adenovirus, it is expected that any one of the serotypes of human or nonhuman adenovirus may be used as the source of the of the fiber gene [*i.e.*, they are all interchangeable]" (page 13, lines 16-20). The only possible exception to the equivalence of **all** the fiber proteins, as disclosed in Wickham *et al.* is the difference between Ad2/Ad5/Ad7[2] and Ad3, since Ad3 utilizes a sialic acid component and sialic acid is found on all higher eukaryotic cells (*e.g.*, page 24, lines 3-10). Wickham *et al.* also teaches alteration of the tropism by insertion of nonnative sequences such as an $\alpha_v\beta_3$-specific RGD peptide (Examples 3, 4, 5, and 6). Wickham *et al.* does not teach that the claimed serotypes can produce a desired tropism or even

[2] Wickham *et al.* teaches a person of ordinary skill in the art that Ad7 is equivalent to Ad5. For example, "the virus in which the native fiber was replaced with a nonnative fiber [Ad7] could also infect cells and express genes **like the parental virus** *in vivo*" (page 29, lines 28-31). Therefore, Wickham *et al.* teaches that Ad7 is equivalent to Ad5, which likely binds to the same receptor [has the same tropism] as Ad2.

that the claimed serotypes have a different tropism. Hence, Wickham *et al.* does not motivate the use of the particular fiber molecules from serotypes 11, 14, 16, 21, 34 and 50 in order to effectuate different tropisms in the resulting adenovirus.

In addition, the mere fact that Wickham *et al.* used a restriction site for the generation of the chimeric fiber proteins does not provide a person of skill in the art with motivation to specifically retain the tail region of the fiber protein. The most that can reasonably be said is that Wickham *et al.* teaches the use of natural restrictions sites, which reside throughout the sequence, and demonstrates that the Nde I site may be used to exchange fiber proteins without detrimental effect on the fiber protein. However, the absence of a detrimental effect does not provide a motivation to retain the tail sequence of the native capsid.

The Office asserts that "Wickham is motivated to do so to utilize a naturally occurring restriction site and the resultant vector has altered tropism and antigenicity (see e.g. example 1)" (page 9 of the Office Action). As discussed herein, the applicants find no showing of altered antigenicity or altered tropism for fiber proteins of the claimed serotypes in Wickham *et al.* Furthermore, as discussed in prior responses, the mere fact that "it is within the ordinary skill of the art to use chimeric fibers in which the tail region of a first adenovirus is fused to a region of a second fiber" does not provide motivation "to do so in order to receive the expected benefit of wide applicability to multiple cell types that Ad 1, 2, 3, 5, 6, 7, 11, 12, 14, 16, 21, 34, 35, 40, 41, or 48 would afford" (page 6 of the Office Action). The cited references do not show "expected benefit of wide applicability to multiple cell types" for the claimed serotypes. In fact, three of the 16 adenovirus serotypes referenced by the Office are not expected to provide different tropisms. Therefore, without recourse to the applicant's specification, it is unclear how the cited references would motivate the selection of the claimed serotypes, which is one of the reasons that the applicants have asserted the inappropriate use of hindsight.

Crystal *et al.* and/or Wickham *et al.*, either alone or in combinantion, do not teach or suggest a recombinant vector based on a native adenovirus containing multiple restriction sites nor the selection of the particular subset of a chimeric fiber proteins, wherein a portion of the

fiber protein is selected from adenoviral serotypes 11, 14, 16, 21, 34, or 50 in order to effectuate a decrease in antigenicity and/or to specify tropism of the resulting adenoviral particle. Further, there is no motivation to combine the teachings of Crystal *et al.*, which actually teaches away from exchanging fiber proteins, in view of Wickham *et al.*

The nonobviousness of the present invention is further demonstrated in the last sentence of the Rea *et al.* publication, which states: "Thus, subgroup B fiber-modified rAd5 constitute a major breakthrough in the exploitation of *ex vivo* rAd-targeted DC [Dendritic Cells] as clinically relevant vaccines and may also be suitable for *in vivo* genetic modification of DC" (Rea *et al.* (2001) Highly Efficient Transduction of Human Monocyte-Derived Dendritic Cells with Subgroup B Fiber-Modified Adenovirus Vectors Enhances Transgene-Encoded Antigen Presentation to Cytotoxic T Cells, *J. Immunol.* 166:5236–5244, 5236) (emphasis added). This proclamation by Rea *et al.*, in a peer reviewed journal, that chimeric, recombinant adenoviral fibers are clinically relevant vaccines further demonstrates the nonobviousness of an embodiment of Applicant's invention. The "major breakthrough" described in Rea *et al.*, published after Applicant's priority date, demonstrates that a person of ordinary skill in the art would not find the Applicant's invention to be obvious. In contrast, Rea *et al.* demonstrates that the present invention satisfies "a long felt need" in the art and provides unexpected results. *Graham v. John Deere*, 383 U.S. 1, 148 USPQ 459 (1966).

The unexpected results of the present invention are further demonstrated in Havenga *et al.*, (2001) Improved Adenovirus Vectors for Infection of Cardiovascular Tissues, *J. Virol.* 75(7):3335-42, 3339, first paragraph, stating that "initial screening, using a few fiber chimeric viruses representing different subgroups of human adenoviruses, resulted in the identification of subgroup B fiber chimeric viruses as being superior to Ad5 for infecting human SMCs and ECs [Smooth Muscle Cells and Endothelial Cells, respectively]." Thus, the present invention was not perceived by persons of ordinary skill in the art to be "expected," rather, it was unexpected that the claimed fiber chimeric viruses would be superior to Ad5.

Havenga *et al.*, (2002) Exploiting the Natural Diversity in Adenovirus Tropism for Therapy and Prevention of Disease, *J. Virol.* 76(9):4612-20, in paragraph 2 of page 4618, state that "a library of 26 different E1-deleted fiber-chimeric adenoviral vectors has been generated, and these vectors are produced on PER.C6 adenovirus packaging cells to titers comparable with standard Ad5 recombinant viruses [increased stability]. This library continues to serve as a platform to identify vectors better suited than Ad5 to genetically modify cells that are considered important target cells in preventive or therapeutic gene transfer strategies. In four distinct medical areas, the increased ability of gene transfer and the potential of the fiber-chimeric vectors are demonstrated." Hence, the claimed recombinant adenoviral vectors have increased stability and continue to provide unexpected and desired alterations in tropism.

These journal articles are published in well respected, peer-reviewed, scientific journals, and given the high standards necessary to qualify for publication, papers demonstrating obvious aspects known in the art are not likely to be accepted for publication. Hence, the present invention provides a major breakthrough in the art, which is nonobvious.[3]

It is therefore respectfully submitted that claims 2-3 and 33-50 are not obvious over Crystal *et al.* in view of Wickham *et al.*, and the rejection of these claims under 35 U.S.C. 103(a) accordingly should be withdrawn. Reconsideration and withdrawal of the rejection are respectfully requested.

[3] *See also*, Havenga *et al.*, (2001) Improved Adenovirus Vectors for Infection of Cardiovascular Tissues, *J. Virol.* 75(7):3335-42, 3335, second paragraph, stating that Ad5.Fib16 has improved infection characteristics on SMCs and ECs compared to the Ad5 and is expected to improve the therapeutic window for the development of gene therapy for the treatment of cardiovascular disease.

Conclusion

It is believed the amendments place claims 2-3 and 33-50 in condition for allowance, and timely issuance of a Notice of Allowance in this case is therefore respectfully requested. Should the Office determine that additional issues remain which might be resolved by a telephone conference, the Examiner is respectfully invited to contact applicants' representative at the telephone number given herein.

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